IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques Dumas et al. Examiner: Yong Soo Chong

Serial No.: 09/458,014 Group Art Unit: 1617

Filed: December 10, 1999 Confirmation No.: 8328

Title: INHBITION OF P38 KINASE USING ACTIVITY SUBSTITUTED HETEROCYCLIC UREAS

REPLY BRIEF

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer mailed March 18, 2010, herewith is Appellant's Reply Brief.

The Reply Brief is presented in response to the following new points of argument raised in the Examiner's Answer:

1) On page 5, lines 5-7 and lines 19-21, of the Examiner's Answer, the breadth of the instant claims is misstated as embracing the treatment of "virtually every disease or disorder that is mediated by p38 kinase," whereas the claims are directed to treating rheumatoid arthritis. As a consequence, the characterization of the prior art on page 5, lines 8-18, is incomplete in that no mention is made of treating rheumatoid arthritis.

Since the characterization of the claimed invention is inaccurate, the characterization of the predictability or unpredictability of the art on page 6, line 20 to page 7, line 20, is also inaccurate. The claimed invention is specifically directed to a method for treating rheumatoid arthritis, not the broad class of diseases "meditated by p38 other than cancer." In addition, there is no evidence the art of treating rheumatoid arthritis is any more predictable or unpredictable than the treatment of other diseases or conditions. The reference, "Goodman & Gilman's The

Pharmacological Basis of Therapeutics," cited in the Examiner's answer provides general information regarding drug-drug interactions presumably applicable to all therapeutic treatments. There is no indication or incite from these general teachings as to whether the treatment of rheumatoid arthritis is predictable or unpredictable.

The degree of experimentation discussed on page 8, lines 13-15, of the Examiner's answer is also mischaracterized in stating, "A large quantity of experimentation would be needed in order to discover what diseases or disorders can be treated by inhibition of p38 and to what extent." The claims herein are directed to treating rheumatoid arthritis so no experimentation would be necessary with regard to the disease which is treated.

The arguments on page 12, lines 1-9, also carry no weight in that they are predicated on the claims "encompassing virtually every disease or disorder that is mediated by p38 kinase."

2) On page 6, lines 11-19 it is alleged "one of ordinary skill in the art would be forced to perform an exhaustive search for the embodiment of any drug having the function recited in the instant claims suitable to practice the invention." Appellants submit these embodiments are already prescribed by the compounds of formula I such that an exhaustive search is not necessary. The *in vivo* studies referred to in the Examiner's answer on page 6, lines 18-19, are not necessary to satisfy the enablement requirement of 35 USC §112, first paragraph. In alleging *in vivo* studies are necessary, the Examiner is requiring that the application meet efficacy and safety standards as set by the FDA to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph (see page 8, lines 18-20, and page 10, lines 13-15). Such a showing is beyond what is necessary to satisfy the enablement requirement of 35 USC §112, first paragraph. As stated in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1442, (Fed. Cir. 1995) with respect to the utility requirement,

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs will prevent any companies from obtaining patent protection on the promising new invention, thereby eliminating an incentive to pursue,

> through research and development, potential cures in any crucial area such as the treatment of cancer.

This rationale translates to prescribing the disclosure necessary to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. As stated in *In re Anthony*, 414 F2d 1383, 162 USPQ 594, 604 (CCPA 1969), "Approval by the FDA, is not a prerequisite for the patenting of a new drug." As to the issue of safety, *In re Anthony* held,

> …Congress has given the responsibility to the FDA, not the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use that they can be introduced in the commercial market, under the conditions prescribed, recommended or suggested in the proposed labeling thereof, as the majority of this court noted in *Hartop*, 135 USPQ at 426, 427.

3) It is alleged on page 11, lines 6-8 that, "The Badger reference is an isolated reference that cannot be taken as the standard for the state of the art concerning inhibition of p38 and the treatment of various diseases." Appellants note that no evidence has been presented to support this allegation and no prior art references have been cited which are inconsistent with the teachings of the Badger reference.

4) It is alleged on page 11, lines 8-13, that the Badger reference "does not provide the missing guidance regarding how to determine which compounds of formula I…..inhibit TNFα to a degree that results in the treatment of rheumatoid arthritis." As stated in the Brief on Appeal, Badger discloses animal models to test the performance of a p38 kinase inhibitor. This reference shows it was routine to test p38 inhibitors as drug candidates in *in vivo* animal models at the time of this invention, as the compounds of formula I were (see page 104 of the specification).

5) It is alleged on page 11, lines 14-15, that "the remaining abstracts were published after the application filing date. The later published articles do not establish that the Examiner erred in determining the state of the art at the time of invention." US Patent Nos. 5,932,576 and US 5,945,418, are ignored in making this statement. The filing dates for these patents are prior to the filing date of this application and demonstrate methods for identifying p38 kinase inhibitors were well known and that

this activity was correlated with the treatment of rheumatoid arthritis. The evidence dated before and after the filing date of this applicator is consistent and demonstrates the characterization of the prior art in the Examiner's Answer is not accurate.

6) On page 11, lines 20-21, the FDA approval of four therapeutics that target TNFα is dismissed as attorney argument. Appellants do not have an official certified copy of the FDA approval letter for these drugs but multiple web sites from different sources, including the FDA, indicate these drugs have been approved, and in the case of Enbrel®, it has been approved prior to the filing date of this application. A copy of a supplemental approval letter from the FDA for Enbrel, not the original, has been submitted with this Reply Brief as an exhibit. It corroborates the approval of Enbrel but not its approval date. With regard to the approval date, an entry in Wikipedia states:

> Amgen's Enbrel, approved in 1998, is the first biologic approved by the FDA to treat rheumatoid arthritis. In 2008, Enbrel achieved $3.6 billion in sales, a growth of 11% over 2007. Enbrel sales increased largely due to an increase in demand, increased average sale price, and Amgen's shift to a wholesale distribution model. Like Humira and Remicade, Enbrel is a biologic and is not currently threatened by generics. However, legislation concerning follow-on biologics will affect Enbrel in the future.

If the FDA approval of the four therapeutics is considered attorney argument, Appellants submit such arguments are well corroborated by third party publications.

7) It is alleged on page 11, lines 19-22, that the teachings in the specification are deficient in spite of these four FDA approved rheumatoid arthritis therapeutics. These four approvals demonstrate it was routine to determine the efficacy and safety of a therapeutic treatment for rheumatoid arthritis. The approval of Enbrel on November 2, 1998 demonstrates such a determination was routine prior to filing the present application. Clearly the claims were enabled by the specification at the time of filing in view of the state of the art. Appellants have demonstrated that the compounds of the invention possess the relevant p38 kinase inhibition and how to use this knowledge in the treatment of rheumatoid arthritis.

In view of the foregoing and the statements made in the Brief on Appeal, Appellants submit the specification provides an enabling disclosure.

For the convenience of the Examiner and Board, a copy of a supplemental approval letter from the FDA for Enbrel has been submitted with this Reply Brief as an exhibit.

With respect to other issues raised in the Examiner's Answer, e.g., the rejection based on the judicially created doctrine of obviousness type double patenting, Appellants stand by their statements in the Appeal Brief.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,
/Richard J. Traverso/

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